The burden of Group B *Streptococcus* worldwide for pregnant women, stillbirths and children

Paper 9: Neonatal encephalopathy with Group B *Streptococcus* disease worldwide: systematic review, investigator group datasets, and meta-analysis

Supplementary information

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Table S1: Case definitions

	Definition	ICD-10 Code
Neonatal encephalopathy	A disturbance of neurological function: newborn brain dysfunction. 'a disturbance of neurological function in the earliest days of life in the term infant manifested by difficulty initiating and maintaining respiration, depression of tone or reflexes, abnormal level of consciousness, and often by seizures' (Leviton& Nelson 1992)	P91.60
Hypoxic-ischemic encephalopathy (HIE)	Encephalopathy in the newborn in the presence of clear evidence of an intrapartum insult including acidosis on cord or early neonatal blood gases and decreased Apgar scores.	P91.60
Therapeutic hypothermia	Total whole body cooling to a core temperature of 33.5C for 72 hours initiated within 6 hours of birth for the treatment of infants with HIE	
Intrapartum-related death	Death as a result of damage to the brain and other vital organs from events occurring around the time of birth	
Birth asphyxia	'Failure to initiate respiration at birth' (ref WHO)	P21
Sepsis	Clinical signs of pSBI *and* GBS-positive culture	A41.9
Meningitis	Clinical signs of pSBI *and* [GBS-positive CSF culture *or* (GBS-positive blood culture *and* CSF pleocytosis)]	G03.9
Pneumonia	Clinical signs (fast breathing, indrawing) *and* radiological evidence of pneumonia *and* GBS-positive blood culture	J18.9

Table S2: Search terms

((Asphyxia Neonatorum [MeSH Terms] OR Hypoxic ischemic encephalopathy [All fields] OR Hypoxic ischemic encephalopathy [All fields] OR Perinatal asphyxia [All fields] OR Intrapartum asphyxia [All fields] OR Intrapartum asphyxia [All fields] OR Intrapartum hypoxia [All fields] OR Brain injury [All fields] OR Neonatal encephalopathy [All fields] OR Cooling) OR Therapeutic hypothermia [All fields] AND (infant or newborn or neonate) [MeSH Terms] OR infant [All fields] OR newborn [All fields] OR newborn infant [All fields] or new-born [All fields] or neonat* [All fields]))
AND
((Streptococcus agalactiae OR Group B streptococc* OR Streptococc* group B) OR Streptococcus agalactiae [MeSH Terms] OR (Infect* OR sepsis OR septic* OR bacter* OR blood culture OR hemoculture OR haemoculture))

Table S3: Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Population	Neonatal encephalopathy *or* Hypoxic-ischemic encephalopathy in term infants	Preterm infants (<35 weeks gestation) Non representative sample
Case definition	Invasive GBS disease Index case <90 days after birth	Cases not pathogen-specific
Laboratory	GBS confirmed by blood / CSF culture *or* PCR or latex agglutination *or* invasive post mortem sample	Skin colonization *or* endotracheal tube tip colonization or lung aspirate
Search	No language or date restrictions	Foreign language papers where it was not possible to obtain English translation
Article type		Case reports

Table S4: Clinical criteria for the definition of neonatal encephalopathy and need for therapeutic hypothermia

Trial/ Score	Criteria for definition of HIE
Sarnat staging, (classifies severity)	Assigned grade 1,2,3 (mild, moderate, severe) HIE depending on findings of each of the following parameters: Muscle tone (normal, mild hypotonia/cortical thumbing, severe hypotonia), Alertness (hyperalert, lethargic, stuporose), Seizures (none, common, uncommon), Reflexes (brisk, mildly brisk, suppression), Primitive reflexes (normal, suppressed, suppression), Autonomic reflexes (sympathetic activation, parasympathetic activation, both systems suppressed), Cranial nerves (weak suck, weak/absent, absent), EEG (normal, first day low voltage then bursting pattern and multifocal electrographic seizures, deep periodic EEG with bursting pattern), Duration (<24 hours, 2-14 days, hours-weeks).
Thompson score for classifying NE	Score of 0-3 for the following parameters: Tone (normal, hyper, hypo, flaccid), Level of consciousness (normal hyperalert/ stare, lethargic, comatose), Fits (none, <3 per day, >2 per day), Posture (normal, fisting/ cycling, strong distal flexion, decerebrate), Moro reflex (normal, partial, absent), Grasp (normal, poor, absent), Suck (normal, poor, absent ± bites), Respiration (normal, hyperventilation, brief apnea, IPPV (apnea)), Fontanelle (normal, full and not tense, tense). Maximum Score = 22. Typically a cut-off of 5 or 6 is used to define NE.
Fenichel's modified criteria for classifying NE	Mild (grade 1) encephalopathy: Irritable or hyperalert, with either poor suck or an abnormality of tone. Moderate (grade 2) encephalopathy: Lethargic, with moderately abnormal tone, poor suck, and depressed Moro and grasp reflexes (seizures were often clinically evident). Severe (grade 3) encephalopathy: Comatose, with severely abnormal tone, absent suck, and brainstem malfunction including impaired respiratory drive. Modifications incorporated observations that infants with mild NE may have signs of not only decreased but increased tone, that seizure activity may not be clinically detectable and therefore cannot serve as a definitive feature in any grading system, and that the inclusion of duration in the clinical definition of a grade renders the scheme contradictory.
NIHCD criteria for cooling	Infants must meet all 3 criteria. A: Infants ≥36 weeks gestation admitted to NICU with a diagnosis of fetal acidosis, perinatal asphyxia, neonatal depression or encephalopathy. B: Umbilical cord/ arterial/ capillary blood pH <7.00 and/or base deficit ≥16 mmol/L within 60 minutes of birth, or pH 7.01-7.15/ base deficit 10-15.9 mmol/L and either an Apgar score of ≤5 at 10 minutes after birth, or assisted ventilation initiated at birth and continued for at least 10 minutes. C: Encephalopathy defined as the presence of 1 or more signs in 3 of the following 6 categories: 1) level of

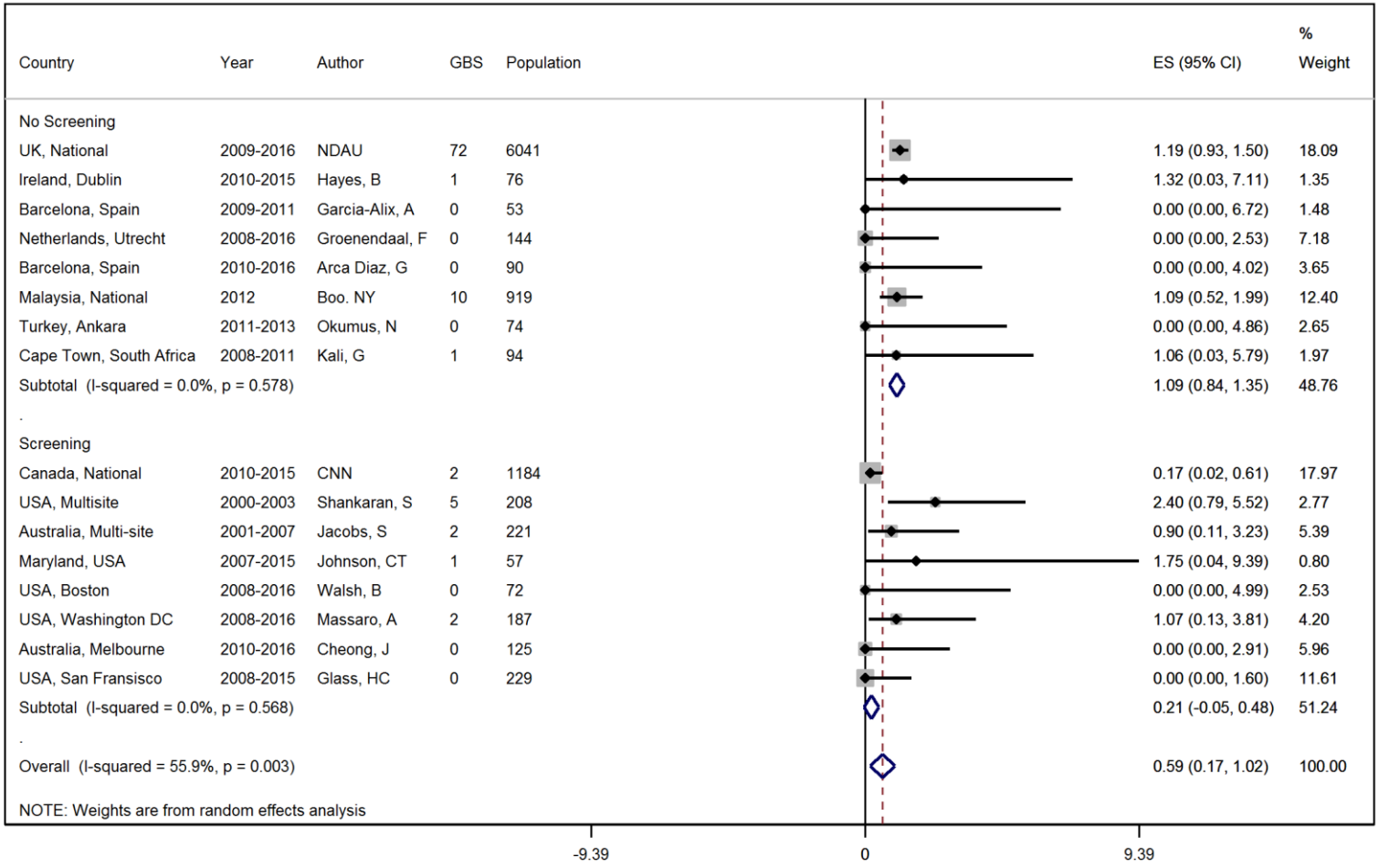
	consciousness (lethargy, stupor or coma), 2) spontaneous activity (decreased, absent), 3) posture (distal flexion, decerebrate), 4) tone (hypotonia, flaccid or hypertonia, rigid), 5) a) primitive reflexes (suck, weak, absent), b) Moro reflex (incomplete, flaccid) and 6) autonomic nervous system a) pupils (constricted, unequal, skew deviation or non-reactive to light), b) heart rate (bradycardia, variable heart rate), c) respiration (periodic breathing, apnea).
TOBY criteria for cooling	Infants must meet all 3 criteria. A: Infants ≥36 weeks gestation and ≤6 hours with one of the following: Apgar score of ≤5 at 10 minutes after birth; continued need for resuscitation 10 minutes after birth; umbilical cord/ arterial/ capillary blood pH <7.00 and/or base deficit ≥16 mmol/L within 60 minutes of birth. B: Moderate to severe encephalopathy consisting of altered state of consciousness (as shown by lethargy, stupor, or coma) and at least one or more of the following; hypotonia, abnormal reflexes, including oculomotor or pupillary abnormalities, an absent or weak suck, clinical seizures. C: At least 30 minutes duration of aEEG recording that shows abnormal background activity or seizures (normal background with some seizure activity, moderately abnormal activity, suppressed activity, or continuous seizure activity).
AAP criteria for cooling	Infants must meet 2 criteria. A: Umbilical cord blood or blood of pH ≤7.0 or a base deficit ≥16 mmol/L within the first hour of birth, history of an acute perinatal event, a 10-minute Apgar score <5, or assisted ventilation initiated at birth and continued for at least 10 minutes. B: Moderate-severe encephalopathy on neurologic examination. If preferential head cooling is used, an abnormal background activity on EEG or aEEG is also required.

Table S5: Outcome of contact with investigator group

Country	Author	Location	Data received (Y/N)	If N, reason why data not received
Australia	Cheong, J	Melbourne	Y	
Australia	Jacobs, SE	ICE trial	Y	
Canada	Wintermark, P	Montreal	Y	
Canada	Shah, P	National	Y	
India	Thayyil, S	Kerala	Y	
India	Thayyil, S	Multi-site	Y	
Ireland	Hayes, B	Dublin	Y	
Malaysia	Boo, NY	Multi-site	Y	
Multi-site	Gunn, A	CoolCap trial	Y	
Multi-site	Azzopardi, D Edwards D	Toby Xenon trial	Y	
Multi-site	Shankaran, S	NICHD cooling trial	Y	
Nepal	Ellis, M	Kathmandu	Y	
Netherlands	De Vries, L	Utrecht	Y	
South Africa	Kali, G	Cape Town	Y	
Spain	Garcia-Alix, A	Barcelona	Y	
Turkey	Okumus.N	Ankara	Y	
Uganda	Tann, C	Kampala	Y	
UK	Gale C	National	Y	
UK	Tann C, Robertson NJ	London	Y	
UK	Thoresen, M	Bristol	Y	
UK/Netherlands	Cowan, F	London/Utrecht	Y	
USA	Glass, H	UCSF, California	Y	
USA	Massaro, A	Washington DC	Y	
USA	Walsh, B	Boston	Y	
USA	Jenster, M	California	Y	
USA	Johnson, CT	Maryland	Y	
Switzerland	Hagmann, C		N	GBS data not collected
UK	Edwards, D Azzopardi, D	TOBY trial	N	GBS data not collected
Australia/New Zealand	ANZNN	National	N	Unable to provide data within time frame
Canada	Chau, V		N	Unable to provide data within time frame
South Africa	Velaphi, S	Johannesburg	N	Unable to provide data within time frame
South Africa	Horn, A		N	Unable to provide data within time frame
UK	Heep, A	Bristol	N	Unable to provide data within time frame
USA	Jenkins, D		N	Unable to provide data within time frame
Australia	Shulzke, S		N	No response
Austria	Simbruner, G		N	No response

Brazil	Galvao, T	N	No response
China	Shao, X	N	No response
China	Cao, C	N	No response
China	Lin, ZL	N	No response
DRC	Naulaers G	N	No response
Egypt	Hassanein, S	N	No response
Greece	Xanthou, M	N	No response
India	Kumar, S	N	No response
Italy	Filippi, L	N	No response
Italy	Buonocore, G	N	No response
Italy	Celik, Y	N	No response
Kuwait	Elbahtiti, A	N	No response
Netherlands	De Haan, T	N	No response
Netherlands	Zonnenberg, IA	N	No response
USA	Angeles, D	N	No response
China	Sun, J	N	Email address not valid/ not successfully received
India	Baht, V	N	Email address not valid/ not successfully received
India	Memon, S	N	Email address not valid/ not successfully received
USA	Christensen, R	N	Email address not valid/ not successfully received

Supplementary Figure S1: *Meta-analysis of Group B Streptococcus disease amongst infants with neonatal encephalopathy presumed to be due to hypoxia-ischemia meeting criteria for therapeutic hypothermia by IAP screening policy*



Supplementary Figure S2: Meta-analysis of mortality before discharge amongst infants with neonatal encephalopathy, by Group B Streptococcus disease

Study or Subgroup		GBS associated NE Events	Total	NE without GBS Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Australia	Jacobs, S	1	3	57	218	4.1%	1.27 [0.25, 6.41]
Canada	CNN	1	2	169	1182	5.4%	3.50 [0.87, 14.08]
International	Gunn, A	1	1	57	233	13.0%	3.05 [1.33, 7.01]
Ireland	Hayes, B	1	1	16	75	11.3%	3.45 [1.39, 8.56]
Malaysia	Boo, NY	4	10	140	909	14.4%	2.60 [1.20, 5.63]
Netherlands	Groenendaal, F	0	4	63	192	1.6%	0.30 [0.02, 4.25]
South Africa	Kali, G	0	1	14	98	1.9%	1.71 [0.15, 19.72]
Uganda	Tann, C	2	3	68	205	13.2%	2.01 [0.88, 4.58]
UK	NDAU	9	72	629	5969	19.9%	1.19 [0.64, 2.20]
USA	Johnson, CT	0	1	3	56	1.7%	4.07 [0.30, 55.16]
USA	Massaro, A	1	2	29	185	5.2%	3.19 [0.77, 13.27]
USA	Shankaran, S	2	5	60	203	8.3%	1.35 [0.45, 4.04]
Total (95% CI)			**105**		**9525**	**100.0%**	**2.07 [1.47, 2.91]**
Total events		22		1305			

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 13.00$, df = 11 (P = 0.29); $I^2 = 15\%$

Test for overall effect: Z = 4.17 (P < 0.0001)